Appendix 4.5.2
Special Considerations for the Development of Biomaterials-Focused Device Prototypes

Biomaterials science and engineering investigates and applies the relationship between the structure of materials, their properties, and their interface with the biological milieu. It is a multidisciplinary area of study that draws together human biology and physiology with elements of applied physics and chemistry, as well as chemical, mechanical, civil, electrical, and materials engineering. If a solution involves a material—whether it be a molecule, polymer, metal, ceramic, or some combination of these—the innovator should clearly define the role the material plays in the device. Key questions to ask upfront include the following: (1) is the device an implant (e.g., an artificial joint) or does it function external to the body (e.g., a sensor, EKG apparatus, or contact lens); (2) if it is an implant, is it a long-term or short-term solution (as with permanent versus temporary pacemakers); and (3) what is the exact anatomic destination? The need for an "active" quality to the device should also be determined; for example, whether it is it degradable (e.g., a tissue engineered scaffold); whether it is "cured" *in vivo* (e.g., a tissue adhesive); whether it will leach some bioactive element (as with drug-eluting stents); or whether it will conduct energy in some form (such as electrical charge, electric field, ultrasound, or radio frequency energy). In addition, the innovator should ask: (4) will the device be made from a polymer, a ceramic, a metal, or biomolecules (e.g., proteins or carbohydrates) or some combination of these; and (5) will it draw from existing, commercially available materials or will it require the development of a new compound? The answers to these questions set the foundation, extent, and expense of subsequent development and ultimately, regulatory evaluation. Expounding on the design parameters in this way based on the combined physical, chemical, mechanical, biological, and electrical property required provides a framework for understanding and engineering the exact functions of the biomaterials science component of the device and the acceptable ranges of its interaction with patient biology.

Once the innovator or team understands what a material needs to do and where, they should seek to identify materials with the performance characteristics to potentially meet these requirements. This can be multifactorial, especially when the requirements are complex, such as finding a material that is tough, but highly elastic, or highly permeable but not impractically fragile. It may be difficult to identify a single material that exhibits all of the desired properties for a particular application. In these cases, blends, alloys, or reinforced composites of materials may be necessary. Various databases are available to assist innovators in their searches, including the ASM Alloy Center Database and the MatWeb Online Materials Information Resource. Innovators can also look at the scientific literature, patents, and regulatory guidelines for ideas on materials that may meet their objectives. From patents, one can identify trends in materials used, as well as materials that may be "blocked" from use by others based on patent protection. Established materials are typically commodities that are often used in innovative medtech concepts, and may be approved for use by the FDA in other applications. However, novel materials, which may be synthesized *de novo* or combined to form new blends or alloys, can contribute another dimension to an intellectual property portfolio.

While this often creates additional risk to the company or project, it may also serve as a barrier to entry by potential competitors by adding further burden to regulatory and testing processes. Information about materials from the technical literature such as the Polymer Handbook can shed light on physical properties and failure modes associated with various substances.

After looking at these various resources, an innovator will be in a position to generate a short list of materials intended to meet the design requirements of the device or device component under development. However, obtaining the desired materials for testing may be difficult or expensive. In these cases, the innovator can try to find a "proxy" material with similar characteristics to the desired material that can be used for proof-of-concept testing. For instance, referring back to the example in chapter 4.5 Concept Exploration & Testing that focuses on filling the left atrial appendage (LAA) with a material such as glue, key design requirements include finding a glue that can anatomically fill the LAA, be delivered through a catheter, and polymerize in less than 20 minutes. If such a glue cannot readily be identified, a substitute material delivered through a catheter could still demonstrate the process and answer some key questions. Though not the ideal solution, it could prove the feasibility of this approach by serving as a proxy for at least one desired trait of the final material. Once some preliminary "book-work" and proof-of-principle testing with proxy materials is completed, it may be necessary to involve someone with specific expertise to perform more complex tests with more advanced materials.

In terms of the specific tests that innovators use to assess different materials, there are many from which to choose. Regulatory guidelines and established standards such as those published by ASTM International and the International Organization for Standardization (ISO) will provide information on the testing and characterization needed if certain materials are used within a device (an important downstream consideration). Among other tests, innovators can use finite element analysis to theoretically model how materials may act/interact in response to mechanical perturbation. Analytical techniques, such as microscopy and chemical analysis/characterization as well as *in vitro* and *in vivo* biocompatibility tests (specifically, the ISO 10993 standard assays) are not only useful but, in most cases, required by regulatory bodies. Depending of the device specifications, these tests often include protocols to test for purity and the presence of potentially toxic leachables (note that having a "clean" interaction surface is critical with this form of testing), oxidative and hydrolytic stability, as well as a thorough evaluation of the mechanical properties, chemical reactivity/stability, bulk material properties, and surface interactions (chemical/biological) of a material.

Additional Resources:

- Buddy D. Ratner, Allan S. Hoffman, Frederick J. Schoen, and Jack Lemons, *Biomaterials Science: An Introduction to Materials in Medicine, Third Edition* (Elsevier, 2013).

- Anthony Atala, Robert Lanza, James A. Thomson, and Robert Nerem, *Principles of Regenerative Medicine, Second Edition* (Elsevier, 2010).
- Robert Lanza, Robert Langer, and Joseph Vacanti, *Principles of Tissue Engineering, Fourth Edition* (Elsevier, 2014).
- J. Brandrup, E.H. Immergut, and E.A. Grulke, *The Polymer Handbook, Fourth Edition* (Wiley-Interscience, 2003).
- L.H. Sperling, *Introduction to Physical Polymer Science, Fourth Edition* (Wiley-Interscience, 2006).
- J.R. Davis, *Handbook of Materials for Medical Devices* (ASM International, 2003).

